Disorders of Calcium and Magnesium

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KEYWORDS

• Calcium • Hypercalcemia • Hypocalcemia • Magnesium • Hypermagnesemia • Hypomagnesemia • Electrolytes • Nutrition

KEY POINTS

- Disorders of calcium and magnesium are associated with an increased mortality, likely due to their effect on normal cardiac and neuronal function.
- Laboratory studies (including confirmatory electrolyte levels) and electrocardiography are the core of initial diagnostic workup in these patients.
- Hypercalcemia and hypermagnesemia are typically handled with fluid resuscitation while hypocalcemia and hypomagnesemia are managed with appropriate replenishment.
- Hypercalcemia of malignancy requires aggressive management with fluids and adjunct medications along with early consultation with appropriate specialists for continued inpatient management.

INTRODUCTION

Calcium and magnesium, both divalent cations, are critical for appropriate function of many processes in the human body, including of the neurologic and cardiovascular systems. Although electrolyte disturbances and disorders often share etiologies and clinical relevance, calcium and magnesium are distinct electrolytes. Therefore, their background, clinical relevance, causes, evaluations, and treatment recommendations are discussed separately in the following sections.

EPIDEMIOLOGY

Calcium and magnesium are often termed the "forgotten cations" because their levels are not routinely evaluated. However, derangements are not uncommon. Hypercalcemia is recognized in approximately 1% to 4% of emergency department and hospitalized patients. Hypercalcemia of malignancy specifically is estimated to affect up to 2.7% of all patients with cancer in the United States.[1] Hypocalcemia is much more common among emergency department and hospitalized patients, with a reported prevalence of 1.5% to 27%.[2–4]

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Hypermagnesemia is rare in the general population, aside from patients with renal failure or iatrogenic hypermagnesemia. In contrast, hypomagnesemia is common although underrecognized in the general population because it is not routinely evaluated for in the outpatient setting. Hypomagnesemia is also common among hospitalized patients, found in 10% to 20% of all hospitalized patients and 60% to 65% of all patients hospitalized to intensive care units.[5]

CALCIUM

Background: Calcium

Calcium (Ca^{2+}) is a bivalent cation, critical for many functions in the human body. This includes the maintenance of normal action potentials in neurons and myocytes, formation of the myosin/actin bridge (needed for muscle contraction), exocytosis of neurotransmitters, and as a crucial component of cell death.[6]

Approximately 98% of the body's calcium is stored in bone, whereas the remaining calcium is found primarily in extracellular fluid. About half of the body's calcium is bound to albumin and other proteins/anions—this form is affected by both blood pH and the concentration of albumin.[7] The remaining half is found in its ionized active form.

Calcium is absorbed in gastrointestinal (GI) tract via both paracellular and transcellular manners. Paracellular absorption from the GI lumen to the blood stream relies on a chemical gradient, and is facilitated by claudins and occludins that regulate membrane permeability.[8] Transcellular absorption from the GI tract occurs by enterocyte brush border uptake via cation channels TPRV5/TPRV6, followed by active transport across the basement membrane into the blood stream by calcium exchangers.[6,8]

Calcium is stored in bone, which acts as a dynamic reservoir for calcium stores, and regulated primarily by parathyroid hormone (PTH). PTH binds osteoblasts, which activates osteoclasts, which leads to the release of calcium into extracellular fluid and ultimately the bloodstream. PTH may also increase the number of osteoblasts.[6]

Calcium reabsorption occurs at several locations in the renal tubular system. Approximately 60% of filtered calcium is reabsorbed in the proximal tubule (PT) and 15% in the thick ascending limb (TAL) of the Loop of Henle.[9,10] Reabsorption at these sites is primarily by paracellular transport, requiring a sodium gradient at the PT and a electrochemical voltage gradient at the TAL. This paracellular transport is facilitated by changes in membrane permeability by claudins at tight junctions, specifically claudin 16 as well as 10, 14, and 19.[11] The remainder of calcium is reabsorbed in the distal convoluted tubule (DCT) by transcellular transport, requiring the cation channels TPRV5/TPRV6.[6,9]

Two hormones play a major role in calcium homeostasis: PTH and vitamin D (calcitriol).[7] Calcitonin has a minor role in human calcium homeostasis. PTH primarily increases calcium by promoting calcium resorption from bone and reabsorption in the kidneys, primarily in the DCT by upregulation of TPRV5/TPRV6 channels.[9] PTH also decreases phosphorus reabsorption in the PT. Calcitriol increases calcium and phosphorus absorption from the GI tract (activated by PTH) and osteoclast activity on bone to maintain homeostatic serum levels.[8]

CLINICAL RELEVANCE OF HYPERCALCEMIA AND HYPOCALCEMIA

Studies have demonstrated that abnormal calcium levels are associated with increased mortality. One study showed that hypercalcemia was associated with a 3 to 3.5 times greater mortality than that of normocalcemic patients in the same hospital system. Hypocalcemia was also associated with a smaller but statistically significant increase in mortality.[2]

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In addition to increased mortality, hypocalcemia has been associated with increased incidence of hypotension and need for transfusion in patients with trauma. In fact, authors in one review even proposed that hypocalcemia be added to the classically taught triangle of death: hypothermia, coagulopathy, and acidosis.[12]

Hypercalcemia is also a risk factor for developing pancreatitis, perhaps due to its part in leading to the activation of enzymes responsible for autodigestion.[13] One study showed that patients with primary hyperparathyroidism are at 10-fold greater risk of pancreatitis compared with the general population.[14]

Data suggest that there may be an inverse correlation between calcium intake and elevated blood pressures.[15] Different mechanisms have been theorized, including PTH acting directly on vascular smooth muscle along with activation of the renin-angiotensin-aldosterone system.[16]

ETIOLOGIES OF HYPERCALCEMIA AND HYPOCALCEMIA

Hypercalcemia

Hypercalcemia is primarily due to hyperparathyroidism or hypercalcemia of malignancy (80%–90% of cases).[17] Either primary hyperparathyroidism or tertiary hyperparathyroidism can cause hypercalcemia. Primary hyperparathyroidism can be due to an adenoma (80%), multiglandular (10%–15%), or rarely parathyroid malignancy (<1%).[7]

Malignancies typically associated with hypercalcemia include squamous cell carcinoma (of head and neck, breast, gynecologic system, kidney, or lung) and multiple myeloma.[18] Hypercalcemia of malignancy occurs by 2 mechanisms. In most solid malignancies, the malignancy itself can secrete PTH-related peptide (PTHrP), which functions physiologically similar to PTH. The second mechanism is the activation of osteoclastic activity, as is classically seen in multiple myeloma.[7]

Other causes of hypercalcemia include granulomatous disease (sarcoidosis, tuberculosis), prolonged immobilization, endocrinopathies (hyperthyroidism, adrenal insufficiency, and others), and genetic causes. Common medications can also cause hypercalcemia such as thiazide diuretics, vitamin D supplements, calcium supplements (Milk-Alkali syndrome), and others.[7,17]

Hypocalcemia

Hypocalcemia has many different causes. It is commonly related to vitamin D deficiency (known as rickets in children), renal failure, or hypoparathyroidism.[19] Hypocalcemia is also seen in massive blood transfusion patients (due to chelation by citrate), and in rhabdomyolysis and tumor lysis syndrome.[12,20] Tumor lysis syndrome causes hypocalcemia in addition to elevated uric acid, hyperkalemia, hyperphosphatemia, and acute kidney injury due to the release of intracellular products from malignant cells; the excess phosphate binds to calcium, leading to hypocalcemia.[20]

There are rare genetic causes of hypocalcemia as well. Pseudohypoparathyroidism, a rare genetic disorder commonly affecting the GNAS1 gene, prevents appropriate calcium reabsorption in the kidney. Similarly, mutations related to Vitamin D metabolism (Vitamin D dependency types I and II) may lead to hypocalcemia.[21]

EVALUATION OF DISORDERED CALCIUM

Signs and Symptoms

Hypercalcemia

Hypercalcemia has a broad range of symptoms, classically referred to by the rhyme "bones, groans, stones, thrones, psychiatric overtones."[22] Musculoskeletal symptoms include bone pain and muscle weakness. Gastrointestinal symptoms are often

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nonspecific, and may include nausea, vomiting, constipation, or even pancreatitis.[1] Renally, hypercalcemia may cause polyuria and nephrocalcinosis; patients with frequent kidney stones should be evaluated for hypercalcemia.[1] In fact, hyperparathyroidism is implicated in up to 5% of patients with nephrocalcinosis.[7] Neuropsychiatric symptoms include delirium and mental status changes, even at lower levels. Less commonly, these patients can present with ataxia and cranial nerve deficits as well as hyporeflexia and hypotonia.[1,7] Hypercalcemia has also been associated with calciphylaxis—the deposition of calcium crystals in microvasculature—particularly in patients with chronic kidney disease.[23]

In emergency department patients, statistically significant associations exist between hypercalcemia and vomiting, polyuria, confusion, hyperparathyroidism, type 1 diabetes, and malignancy.[4]

Hypocalcemia

Contrary to hypercalcemia, hypocalcemia causes hyperexcitation of both neuronal and muscle cells, which ultimately leads to spasms and paresthesias.[19] These patients are also at risk for cardiovascular complications, such as arrhythmias, and many other nonspecific symptoms.

Classically, the Chvostek sign and Trousseau sign are associated with hypocalcemia. The Chvostek sign is the spontaneous contraction of the facial nerve when percussed, often with a reflex hammer.[24] Unfortunately, recent data show this sign is neither sensitive nor specific: 29% of patients with hypocalcemia lack this sign, and 25% of patients with this sign have normocalcemia.[25] Some research has suggested it can even be seen in patients with hypercalcemia.[24] The Trousseau sign (carpopedal spasm with inflation of a blood pressure cuff, caused by local ischemia) is far more sensitive and specific, estimated to be present in 94% of cases of hypocalcemia.[26,27]

In emergency department patients, statistically significant associations exist between hypocalcemia and vomiting, perioral numbness, hand or foot spasm, presence of calcium or phosphate supplementation, and chemotherapy.[4]

Electrocardiography

Calcium influx represents stage 2 of the cardiac action potential, also known as the plateau phase.[28] Therefore, calcium balance will greatly affect cardiac action potential length, particularly between depolarization (QRS complex) and repolarization (T wave) on an electrocardiogram.

Hypocalcemia therefore leads to prolongation of the QT interval (**Fig. 1**). Because hypocalcemia leads to excess depolarization and a prolonged repolarization time, the QT prolongation will specifically show a prolonged ST segment with a T wave of normal duration and morphology.[29] As with other cases of QT prolongation, patients with hypocalcemia are at risk for torsades de pointes and other ventricular arrhythmias. However, they seem to occur less commonly than with hypokalemia or hypomagnesemia.[29]

Conversely, hypercalcemia will cause shortening of the QT interval without changes to T wave morphology (**Fig. 2**). Hypercalcemia is rarely associated with dysrhythmias such as bradydysrhythmias.[29] J waves (also known as Osborne waves), although commonly associated with hypothermia, can also be seen in hypercalcemia, and are thought to be related to changes in ion channel permeability.[30]

Laboratory Testing

Normal total calcium levels range from 2.15 to 2.60 mmol/L (8.0–10.4 mg/dL).[1] Ionized calcium levels, the metabolically active form, typically range from 1.0 to 1.4 mmol/L

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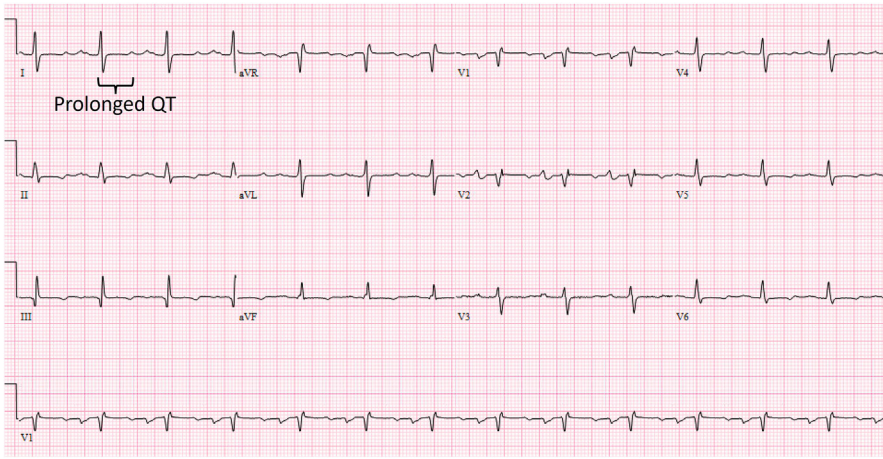

Fig. 1. Electrocardiogram of a patient with a calcium level of 1.3 mmol/L (5.4 mg/dL) demonstrating a prolonged QT interval. (*Courtesy* of Amal Mattu, MD.)

(4.0–5.6 mg/dL). It has been taught that serum calcium must be corrected for the serum albumin level.[1] One of the more common formulae is as follows:[31]

Corrected calcium = 0.8 × (normal albumin level − patient's albumin level) + serum calcium.

However, recent literature has questioned the accuracy of this formula. One study showed that this adjusted calcium formula overcorrects in settings of renal dysfunction and albumin levels less than 0.45 mmol/L (3 g/dL).[32] Another study found that unadjusted calcium levels are superior in diagnostic accuracy compared with the application of correction formulas.[33] Especially critically ill patients and those with severe albumin abnormalities should have an ionized calcium level measured.[7,33] However, pH may affect the ionized calcium measurement.[7]

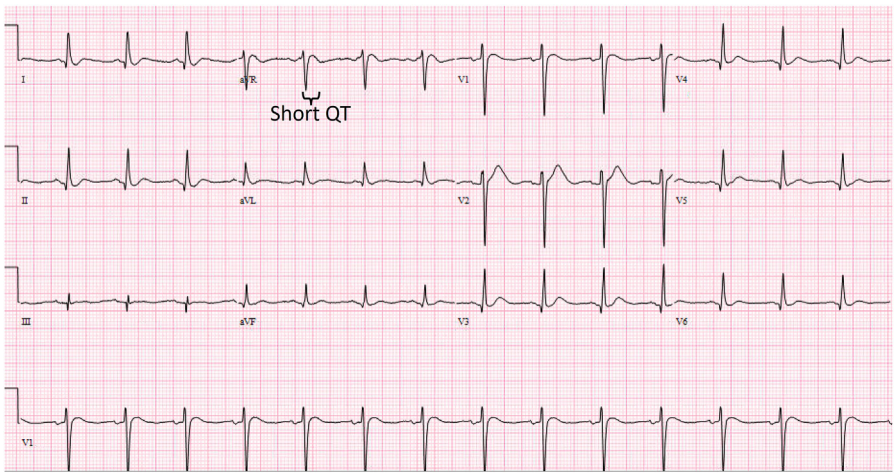

Fig. 2. Electrocardiogram of a patient with a calcium level of 3.8 mmol/L (15.1 mg/dL) demonstrating a short QT interval. (*Courtesy* of Amal Mattu, MD.)

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If hypercalcemia or hypocalcemia is found, a repeat measurement of calcium, both total and ionized if available, should be drawn for confirmation.

Additional laboratory studies to obtain in cases of hypercalcemia include phosphate, vitamin D, PTH, PTHrP (if concerned for malignancy), renal function, and alkaline phosphatase level (if concerned for bone lysis).[17] The primary diagnostic division is to determine whether the hypercalcemia is PTH dependent or PTH independent.[7,17] An elevated PTH level would suggest hyperparathyroidism, whereas a suppressed PTH level would suggest other causes such as malignancy, hypervitaminosis D, and granulomatous disease.[7,17]

In cases of hypocalcemia, an albumin level should be collected, although the questionable accuracy of hypocalcemia with hypoalbuminemia should be considered as mentioned previously. Magnesium, phosphate, renal function, and vitamin D levels should also be obtained for a complete workup. As in hypercalcemia, a PTH level should be collected to determine if the hypocalcemia has an appropriate compensatory increase in PTH levels.[19] Low/normal PTH levels in the setting of hypocalcemia would suggest hypomagnesemia or hypoparathyroidism as the cause. Elevated PTH levels with hypocalcemia show appropriate compensation by the parathyroid glands and would suggest vitamin D deficiency (confirmed by laboratory measurement), renal failure, or genetic causes such as pseudohypoparathyroidism.[19] Concern for tumor lysis syndrome should prompt obtaining renal function in addition to uric acid, calcium, potassium, and phosphate levels to confirm diagnosis.[20]

In cases where cause is unclear for either hypercalcemia or hypocalcemia, 24-hour urinary calcium level can be measured and be followed up in the outpatient setting.[17,21] However, this is typically not done in the emergency department setting.

RECOMMENDATIONS FOR THE TREATMENT OF HYPERCALCEMIA AND HYPOCALCEMIA

Hypercalcemia

Hypercalcemia generally requires emergent treatment only when patients are symptomatic or have a total calcium level above 3.5 mmol/L (14 mg/dL).[34] Otherwise, patients can be managed with adequate oral hydration and close outpatient follow-up after initial diagnostic workup. The patient's medication list should be reviewed, and common culprits of hypercalcemia should be held until patient can be followed up as an outpatient.[17]

Those that are more critically ill (typically due to hypercalcemia of malignancy) require aggressive intravenous volume resuscitation; these patients are often hypovolemic from polyuria due to hypercalcemia. It is not uncommon for patients to receive 3 to 6 L of intravenous fluids in the initial 24 hours of their treatment.[7] The rate of fluids should always be considered in the context of the patient's comorbidities (cardiomyopathy and hypoalbuminemia). Some authors have advocated that fluid rates of 150 to 200 mL/h can be considered for those without significant cardiovascular comorbidities.[17]

Although previously a hallmark of management, furosemide has recently come into question as a routine treatment in hypercalcemia.[35] There is limited evidence to suggest patients should routinely receive furosemide unless hypervolemic. Furosemide does not clinically seem to increase calcium excretion, and furosemide may cause worsening hypercalcemia in euvolemic patients by causing volume contraction.[7,34]

Additional therapies can be initiated, usually in consultation with oncology and/or endocrinology. Bisphosphonates (pamidronate and zoledronic acid), first-line agents in hypercalcemia of malignancy, are critical in blocking bone resorption into the

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bloodstream. Calcitonin may be considered, particularly in the initial treatment; however, it is associated tachyphylaxis along with hypersensitivity reactions. Corticosteroids and denosumab (a RANKL monoclonal antibody against osteoclast activity) can also be used after discussion with specialists, depending on the cause and response to initial treatment.[34]

As a last resort, dialysis can be used for refractory hypercalcemia in patients that have acute encephalopathy, chronic kidney disease or end-stage renal disease, or are unable to handle aggressive fluid resuscitation.[34]

Hypocalcemia

After confirmation, hypocalcemia should be treated based on the severity of symptoms.

In the stable patient, oral calcium supplementation can be initiated. Formulations include calcium carbonate and calcium citrate, typically initially dosed at 500 to 1000 mg three times daily. Magnesium supplementation should also be considered, especially in patients with hypoparathyroidism.[36]

Critically ill patients, defined as those with symptomatic hypocalcemia or total calcium level less than 2 mmol/L (7.5 mg/dL), require intravenous repletion of calcium.[19] Two forms exist: a 10 mL ampule of 10% calcium gluconate (90 mg elemental calcium) and a 10 mL ampule of 10% calcium chloride (272 mg elemental calcium).[37] Calcium gluconate is safe to give through peripheral veins, whereas calcium chloride should be restricted to central veins, unless the patient is in extremis. These patients should also receive intravenous magnesium supplementation if needed, because hypomagnesemia contributes to hypocalcemia. Patients should be monitored by telemetry because calcium and magnesium replenishment, especially in critically ill patients, can be complicated by dysrhythmias.[19,37]

If patients are found to be Vitamin D deficient, they should be started on supplementation with oral vitamin D. Doses start at either 400 IU daily for mild cases or 50,000 IU weekly in more severe cases.[19]

In cases of massive transfusion, there is no clear consensus on calcium supplementation. Some sources recommend giving 1 g of calcium supplementation for every 3 units of blood products with the goal of maintaining an ionized calcium level of greater than 0.9 to 1.2 mmol/L.[12]

MAGNESIUM

Background: Magnesium

Magnesium (Mg^{2+}) is the fourth most abundant cation in the human body and the second most abundant intracellular cation within human cells.[5] Magnesium has been implicated as a cofactor in more than 600 enzymatic reactions in the human body, acts as a calcium antagonist, and is involved in processes such as lipid and protein metabolism, synthesis of transporters and adenosine triphosphate, bone metabolism/formation, and PTH secretion.[38–40]

Total body magnesium is distributed as follows: 60% in bones, 38% in soft tissues, and 1% to 2% in the extracellular fluid.[41] The main sources of dietary magnesium include green leafy vegetables, unprocessed grains, nuts, seafood, and beans, and variably dietary supplements and water.[40,42] It is estimated that nearly 70% of US adults consume less than the recommended daily intake of magnesium.[38,39,43]

The balance of magnesium in the human body is maintained by intestinal absorption, storage in bone, and renal excretion.[5,38,39] Magnesium is also eliminated with other electrolytes via sweat but this is only relevant under extreme conditions.

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Under normal physiologic conditions, 30% to 50% of dietary magnesium intake is absorbed via the intestines, although this percentage of absorption can increase to 80% if one has a deficiency of magnesium intake.[38,41] Magnesium is absorbed in the intestines by both passive and active mechanisms. Passive absorption occurs via paracellular transport in the small intestine (jejunum and ileum) and is proportional to dietary intake.[38,39] This operates by electrochemical gradient along with water and other solutes and is responsible for approximately 80% to 90% of magnesium absorption under normal physiologic conditions.[41] Substances that increase magnesium solubility (such as vitamin D) favor its absorption, whereas substances that form insoluble complexes with magnesium (such as phosphates) decrease its absorption.[39,44] Active transport occurs via transcellular transport in the cecum and colon through the luminal TRPM 6 and TRPM 7 channels and the basolateral Na/Mg exchanger, and operates mostly under conditions of low magnesium intake (magnesium deficiency).[39,41] With increasing levels of dietary magnesium intake, active absorption rates decrease.

Magnesium is primarily stored in bone, which functions as a magnesium reservoir to stabilize its serum concentration.[39] A deficiency in magnesium results in decreased bone formation.[38]

The glomeruli filter approximately 2400 mg of magnesium daily, with the nephron recovering 95% to 99% of this filtered magnesium.[38] The kidneys conserve magnesium in response to a magnesium deficit, and increase their excretion of magnesium in response to a surplus. Approximately 20% to 30% of magnesium is reabsorbed in the PT, occurring mostly via passive paracellular transport (which requires sodium and water to drive transport).[38,39] The TAL of the Loop of Henle is where most magnesium reabsorption occurs—approximately 65% of filtered magnesium—via voltage gradient-dependent passive paracellular transport (which depends on tight junction [claudin] permeability).[38,39] Among other factors, magnesium reabsorption in the TAL is increased by glucagon, PTH, calcitonin, and insulin, whereas magnesium reabsorption is decreased by hypercalciuria, hypophosphatemia, metabolic acidosis, increased catecholamine levels, and osmotic diuretics.[39] The remaining 5% to 10% of magnesium reabsorption takes place in the DCT by active transcellular transport via the TRPM 6 channel, which may be influenced by hormonal fluctuations, including estrogen.[5]

CLINICAL RELEVANCE OF HYPERMAGNESEMIA AND HYPOMAGNESEMIA

Specifically in patients requiring hemodialysis, hypermagnesemia may play a protective role against the development of vascular calcifications, and hypomagnesemia has been shown to be a significant predictor for all-cause mortality.[5]

There are many other cardiovascular, neurological, psychiatric, pulmonary, renal, hematologic, and endocrine disorders for which hypomagnesemia is thought to be implicated in the development or severity of the disease state, or for which magnesium is thought to be a viable treatment option. This may be due to magnesium's action as a natural calcium channel blocker and vasodilator, as an antagonist of sodium, as an N-methyl-D-aspartate (NMDA) receptor blocker, as a natural anti-inflammatory and antioxidative agent, or due to other properties.[5,38] However, the data remain largely inconclusive and more research is necessary. Some of these disease states include hypertension, arrhythmias, atherosclerosis and dyslipidemia, migraine, chronic pain and fibromyalgia, perioperative pain, stroke, epilepsy, traumatic brain injury, Alzheimer and Parkinson diseases, depression and other mood disorders, asthma, diabetes, metabolic disorders, sickle cell disease, osteoporosis, cancers, and general inflammation.[39,44–53]

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ETIOLOGIES OF HYPERMAGNESEMIA AND HYPOMAGNESEMIA

Hypermagnesemia

Hypermagnesemia is rare in humans, occurring mostly in individuals with renal insufficiency or due to iatrogenic causes.[54] No genetic causes of hypermagnesemia have been identified.[38] The kidneys are effective at excreting excess magnesium, and hypermagnesemia is almost exclusively seen in individuals whose creatinine clearance is less than 30 mL/min, especially either in those individuals who are given magnesium-containing drugs (such as laxatives or antacids) or in those individuals who take magnesium-rich supplements (such as Epsom salts).[38,55] Iatrogenic hypermagnesemia is also encountered in patients with preeclampsia undergoing seizure prophylaxis with magnesium sulfate. Other conditions in which hypermagnesemia may be seen include patients with hemolysis, lithium intoxication, adrenal insufficiency, and hyperparathyroidism.[5]

Hypomagnesemia

Hypomagnesemia may be due to dietary deficiency, defective gastrointestinal absorption, or increased magnesium excretion (primarily by the kidneys).

Alcohol is an important cause of hypomagnesemia, and approximately 30% of patients with alcohol abuse have hypomagnesemia. This occurs due to malnutrition resulting in dietary magnesium deficiency, chronic diarrhea resulting in gastrointestinal malabsorption, and increased magnesium excretion.[5] Thiamine deficiency is also common in patients with chronic alcohol use, and magnesium is an important cofactor in thiamine metabolism.[56]

Gastrointestinal malabsorption and losses are commonly encountered in patients with secretory diarrhea, enteritis, acute pancreatitis, and bariatric surgery.[5,41]

Hypomagnesemia resulting from renal excretion has many causes. Some of these are due to genetic causes, such as Gitelman/Bartter syndrome (genetic salt-wasting conditions), defects in claudin or TRPM 6 expression, and defects in epidermal growth factor signaling.[5] Diseases such as diabetes may also cause hypomagnesemia when poorly controlled.[41] However, hypomagnesemia may also be due to mechanical issues with the kidneys (such as with postobstructive diuresis) or intrinsic renal pathologic conditions (such as with acute tubular necrosis).

A variety of different medications is directly responsible for hypomagnesemia.[57,58] Medications such as insulin and epinephrine cause intracellular shift of magnesium, leading to lower serum magnesium levels. Laxative abuse, proton pump inhibitors, and metformin cause hypomagnesemia by promoting gastrointestinal losses. Multiple antibiotics/antifungals/antivirals (including aminoglycosides, amphotericin B, and rapamycin) and antineoplastic agents (including carboplatin, cisplatin, and monoclonal epidermal growth factor receptor inhibitors such as cetuximab) cause hypomagnesemia by both promoting gastrointestinal losses and increasing urinary magnesium excretion. Calcineurin inhibitors, diuretics (thiazides and furosemide), and digoxin cause hypomagnesemia by increasing urinary magnesium excretion. Massive transfusions (chelation by citrate), foscarnet, bisphosphonates, and patiromer have also been implicated in hypomagnesemia.[57,58]

Athletes and elderly individuals seem particularly susceptible to hypomagnesemia. Athletes oftentimes consume diets with inadequate mineral amounts, and have more profound mineral losses in their urine and sweat.[39] Elderly individuals are at risk, both from their comorbidities and medication side effects.[39]

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EVALUATION OF DISORDERED MAGNESIUM

Signs and Symptoms

Hypermagnesemia

Hypermagnesemia is responsible for a spectrum of neurologic, cardiovascular, and pulmonary findings.[5] As serum magnesium levels increase greater than 2 mmol/L (4.9 mg/dL), patients may experience lethargy, drowsiness, flushing, nausea and vomiting, and diminished deep tendon reflexes.[38] As levels increase greater than 3 mmol/L (7.3 mg/dL), patients may experience somnolence, loss of deep tendon reflexes, hypotension, and electrocardiographic changes (see later discussion). As levels increase greater than 5 mmol/L (12.2 mg/dL), patients may experience complete heart block, cardiac arrest, apnea, paralysis, coma, and death.[38] Other symptoms of hypermagnesemia may include generalized weakness and impaired respirations. For mothers with preeclampsia receiving magnesium sulfate for seizure prophylaxis, neonatal depression, hypotonia, and low Apgar scores may also occur with maternal serum magnesium levels greater than 3.5 mmol/L (8.5 mg/dL).[5]

Hypomagnesemia

Hypomagnesemia oftentimes go underrecognized due to its initial vague and nonspecific symptoms when serum magnesium levels decline to 0.5 to 0.7 mmol/L (1.2–1.7 mg/dL).[5] Patients may experience neuromuscular irritability, leading to symptoms such as tremors, muscle weakness, nystagmus (downbeat vertical), athetosis, confusion, hallucinations, and depression.[5,41] This degree of hypomagnesemia is oftentimes also associated with hypocalcemia and hypokalemia.[38] As levels decline to less than 0.5 mmol/L (1.2 mg/dL), patients experience more severe symptoms including tetany, seizures, psychosis, and significant arrhythmias (atrial fibrillation, supraventricular tachycardia, torsades de pointes ventricular tachycardia).[38,41]

Electrocardiography

Neither hypermagnesemia nor hypomagnesemia produce specific or pathognomonic findings on electrocardiography, and electrocardiographic changes are oftentimes due to the accompanying derangements in other electrolytes (potassium and calcium).[29,58,59] However, it has been observed that hypomagnesemia may result in QRS complex widening, T-wave changes (peaking or flattening), prolongation of the QT and PR intervals, and dysrhythmias such as atrial fibrillation, premature ventricular contractions, and ventricular dysrhythmias (torsades de pointes (**Fig. 3**)).[29,41,58,59] Hypermagnesemia has been associated with atrioventricular nodal blocking resulting in complete heart block.[41,58]

Laboratory Testing

Magnesium exists as protein-bound (20%–30%), complexed to another ion (such as bicarbonate, citrate, sulfate, or phosphate; 5%–15%), or ionized/free (55%–70%).[41] Although ionized magnesium is the biologically active form, ionized magnesium levels are not commonly determined.[38]

Normal serum magnesium levels are between 0.76 and 1.05 mmol/L (1.8–2.6 mg/dL), with hypomagnesemia generally defined as a serum magnesium level less than 0.7 mmol/L (1.7 mg/dL) and hypermagnesemia generally defined as a serum magnesium level greater than 1.1 mmol/L (2.7 mg/dL).[38,54] Conversely, magnesium deficiency refers to a magnesium intake less than the minimal recommended dietary levels.[5] It is possible to be hypomagnesemic without being magnesium deficient and vice versa.

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Fig. 3. Electrocardiogram of a patient with a magnesium level of 0.5 mmol/L (1.2 mg/dL) who developed torsades de pointes because of their hypomagnesemia. (*Courtesy* of Amal Mattu, MD.)

RECOMMENDATIONS FOR THE TREATMENT OF HYPERMAGNESEMIA AND HYPOMAGNESEMIA

Hypermagnesemia

Patients who are found to have symptomatic hypermagnesemia or magnesium levels greater than 3 mmol/L (7.3 mg/dL) should be treated with airway management, continuous cardiac monitoring, and an infusion of intravenous calcium (to antagonize the cardiovascular and neuromuscular effects of magnesium), generally recommended as 100 to 200 mg over 5 to 10 minutes.[38,41,58] In extremely severe cases of hypermagnesemia, hemodialysis may also be used to acutely lower magnesium levels. Mild or asymptomatic hypermagnesemia can be managed with adequate oral hydration and outpatient follow-up.

Hypomagnesemia

Hypomagnesemia is generally treated as an outpatient with oral magnesium supplementation, although this may cause diarrhea at higher doses. Many forms of magnesium supplementation exist, with no universal recommendation. Intravenous supplementation may be more effective and is generally indicated when clinical symptoms are present, with magnesium levels less than 0.50 mmol/L (1.2 mg/dL), or when oral supplementation is not well tolerated.[38,41,57]

The "rule of thumb" is that administration of 1 g of intravenous magnesium will increase serum magnesium concentration by 0.08 mmol/L (0.2 mg/dL) within approximately 1 day.[58] In practice, treatment of hypomagnesemia usually starts as a 2-g bolus infusion of intravenous magnesium (in the form of magnesium sulfate) over 5 to 60 minutes, followed by a continuous infusion (4–8 g over 12–24 hours), targeting a serum magnesium level of at least 0.62 mmol/L (1.5 mg/dL).[41,58,60] Doses of up to 6 g magnesium sulfate may be administered over an 8 to 12-hour period, whereas higher doses should be administered over 24 hours or more.[60] Approximately 50%

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of infused magnesium is rapidly renally excreted and, therefore, has only transient effects.[41]

Patients with severe hypomagnesemia or those with concurrent hypokalemia should also be supplemented with potassium. Amiloride (to prevent potassium secretion) may also be considered for these patients.[38]

Other Indications for Magnesium Supplementation

Preeclampsia

Magnesium is recommended as seizure prophylaxis for pregnant and postpartum patients with preeclampsia. Literature suggests loading doses of 4 to 6 g intravenous magnesium over 10 to 15 minutes, followed by maintenance doses of 1 to 3 g per hour.[58,61] Target serum magnesium levels for seizure prophylaxis in preeclampsia are 2.5 to 4 mmol/L (6.1–9.7 mg/dL), and additional caution should be used in patients with underlying decreased renal function.[41]

Torsades de pointes

Magnesium is recommended in the management of torsades de pointes (polymorphic ventricular tachycardia associated with a long QT interval) to prevent reinitiation of the arrythmia.[62] Literature recommends a loading dose of 2 g intravenous magnesium over 2 to 15 minutes, followed by a continuous infusion.[58] There may also be some benefit to a bolus and infusion of magnesium for the treatment of other arrhythmias, such as atrial fibrillation.[63]

Asthma

Magnesium has been shown to improve pulmonary function and reduce the need for hospitalization in patients with severe asthma exacerbations.[64,65] Literature suggests adult dosing of 2 g intravenous magnesium, repeated every 20 minutes for up to 3 total doses.[66]

Analgesic

Magnesium may have a role as an adjuvant analgesic for various acute and chronic pain syndromes, including the control of perioperative pain, neuropathic pain, muscle cramps, and migraines.[53,67,68] This is primarily thought to because of magnesium's inhibitory action at NMDA receptors. However, literature reports varied efficacy and there is no universally accepted dose or route for the use of magnesium as analgesia. Perioperative studies have suggested a bolus dose of 30 to 50 mg/kg intravenous magnesium.[69]

SUMMARY

Disorders of calcium and magnesium are often difficult to diagnose because symptoms tend to be nonspecific at their onset. However, prompt correction of these electrolyte abnormalities is critical to prevent cardiovascular and neurologic complications. Etiologies of these electrolyte disorders range from mild medication effects and dietary deficiencies to occult malignancy and unbalanced trauma resuscitation. Although rarer in an acute setting than other electrolyte abnormalities, keep a high level of suspicion for these "forgotten cation" derangements. Screening for disordered calcium and magnesium in the emergency department should be considered particularly in critically ill patients, in those with significant gastrointestinal losses (vomiting and diarrhea), and in those with comorbidities (especially renal disease and malignancy). Replenishment of low calcium and magnesium levels should be initiated in the emergency department after identification.

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CLINICS CARE POINTS

- Measurements of ionized calcium and serum magnesium are the gold standards in diagnosing disordered states of calcium and magnesium.
- Hypocalcemia and hypomagnesemia will generally require intravenous supplementation if diagnosed in the emergency department.
- Symptomatic or severe hypercalcemia and hypermagnesemia require aggressive care: fluid resuscitation and close consultation with endocrinology/oncology for hypercalcemia, and fluid resuscitation with calcium infusion for hypermagnesemia.
- Hypocalcemia and hypomagnesemia should always be considered and evaluated for in patients with prolonged QT intervals on electrocardiography.

DISCLOSURE

The authors have no financial disclosures.

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